# Phase I Trial of a Tablet Formulation of Pilaralisib, a Pan#Class I PI3K Inhibitor, in Patients with Advanced Solid Tumors

The Oncologist®

Clinical Trial Results

# Phase I Trial of a Tablet Formulation of Pilaralisib, a Pan-Class I PI3K Inhibitor, in Patients with Advanced Solid Tumors

Gerald Edelman,[a] Jordi Rodon,[b] Joanne Lager,[c] Christelle Castell,[d] Jason Jiang,[e] Eliezer M. Van Allen,[f,h] Nikhil Wagle,[f,h] Neal I. Lindeman,[i] Lynette M. Sholl,[i] Geoffrey I. Shapiro[g]

[a]Mary Crowley Medical Research Center, Dallas, Texas, USA; [b]Vall d'Hebron University Hospital and Universitat Autonoma de Barcelona, Barcelona, Spain; [c]Sanofi, Cambridge, Massachusetts, USA; [d]Sanofi, Vitry sur Seine, France; [e]Sanofi, Bridgewater, New Jersey, USA; [f]Center for Cancer Precision Medicine and [g]Early Drug Development Center, Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [h]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA; [i]Center for Advanced Molecular Diagnostics, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts, USA

## Trial Information

- **ClinicalTrials.gov Identifier**: NCT00486135
- **Sponsor(s)**: Sanofi, Exelixis
- **Principal Investigator**: Geoffrey I. Shapiro
- **IRB Approved**: Yes

## Lessons Learned

- A phase I study of the pan-class I phosphoinositide 3-kinase inhibitor pilaralisib (in capsule formulation) in advanced solid tumors established the maximum tolerated dose as 600 mg once daily.
- The current study investigated pilaralisib in tablet formulation.
- Pilaralisib tablets were associated with a favorable safety profile and preliminary antitumor activity.
- Based on pharmacokinetic data, the recommended phase II dose of pilaralisib tablets was established as 400 mg once daily.

## Abstract

***Background.*** A phase I trial of pilaralisib, an oral pan-class I phosphoinositide 3-kinase (PI3K) inhibitor, established the maximum tolerated dose (MTD) of the capsule formulation in patients with advanced solid tumors as 600 mg once daily. This phase I study investigated pilaralisib in tablet formulation.

***Materials and Methods.*** Patients with advanced solid tumors received pilaralisib tablets (100–600 mg once daily). Primary endpoints were MTD and safety; secondary and exploratory endpoints included pharmacokinetics (PK), pharmacodynamics, and efficacy.

***Results.*** Twenty-two patients were enrolled. No dose-limiting toxicities (DLTs) were reported. The most common treatment-related adverse events were diarrhea (40.9%), fatigue (40.9%), decreased appetite (22.7%), and hyperglycemia (22.7%). Pilaralisib plasma exposure did not appear to increase dose-proportionally. Steady-state exposure was higher with pilaralisib tablet formulation at 400 mg than with pilaralisib capsule formulation at 400 or 600 mg (mean area under the curve [$AUC_{0-24}$] 2,820,000 ng × h/mL vs. 2,653,000 and 1,930,000 ng × h/mL, respectively). Of 18 evaluable patients, 2 (11.1%) had a partial response (PR).

***Conclusion.*** Pilaralisib tablets were associated with a favorable safety profile and preliminary antitumor activity. MTD was not determined. The recommended phase II dose for pilaralisib tablets, based on PK data, was 400 mg once daily. ***The Oncologist*** 2018;23:401–e38

## Discussion

The PI3K pathway has been implicated in the pathogenesis of solid tumors, and several PI3K inhibitors in development have shown evidence of clinical antitumor activity. Pilaralisib (SAR245408) is a highly selective and reversible pan-class I PI3K inhibitor. A phase I study of pilaralisib capsules in 69 patients with advanced solid tumors (NCT00486135) established the MTD as 600 mg once daily. In addition, pharmacodynamic inhibition of the PI3K pathway and one PR were observed. The current study investigated pilaralisib in tablet formulation.

Twenty-two patients were enrolled and received at least one dose of pilaralisib tablets. The median duration of exposure was 56.0 days. No DLTs were observed, and the MTD was not established. Safety findings with pilaralisib tablets were generally consistent with previous findings in patients with solid tumors who received the capsule formulation. The most common treatment-related toxicities included gastrointestinal toxicities, fatigue, and hyperglycemia (Table 1), consistent with other PI3K inhibitors in clinical development.

Correspondence: Gerald Edelman, M.D., Mary Crowley Medical Research Center, Medical Surgical Clinic of Irving, Dallas, Texas 75061, USA. Telephone: 972-253-4245; e-mail: sonatduke@yahoo.com Received November 14, 2017; accepted for publication December 12, 2017; published Online First on March 28, 2018.  http://dx.doi.org/10.1634/theoncologist.2017-0691

**Table 1.** Treatment-related adverse events occurring in >5% of patients treated with pilaralisib tablets once daily (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0)

| | 100 mg ($n = 3$) | | 200 mg ($n = 6$) | | 250 mg ($n = 3$) | | 400 mg ($n = 7$) | | 600 mg ($n = 3$) | | Total ($n = 22$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Adverse events** | **Any grade, *n* (%)** | **Grade ≥3, *n* (%)** | **Any grade, *n* (%)** | **Grade ≥3, *n* (%)** | **Any grade, *n* (%)** | **Grade ≥3, *n* (%)** | **Any grade, *n* (%)** | **Grade ≥3, *n* (%)** | **Any grade, *n* (%)** | **Grade ≥3, *n* (%)** | **Any grade, *n* (%)** | **Grade ≥3, *n* (%)** |
| Diarrhea | 1 (33.3) | 0 | 2 (33.3) | 1 (16.7) | 1 (33.3) | 0 | 2 (28.6) | 0 | 3 (100.0) | 0 | 9 (40.9) | 1 (4.5) |
| Fatigue | 2 (66.7) | 0 | 1 (16.7) | 0 | 3 (100.0) | 0 | 2 (28.6) | 0 | 1 (33.3) | 0 | 9 (40.9) | 0 |
| Decreased appetite | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 3 (42.9) | 0 | 1 (33.3) | 0 | 5 (22.7) | 0 |
| Hyperglycemia | 1 (33.3) | 0 | 1 (16.7) | 0 | 1 (33.3) | 0 | 1 (14.3) | 0 | 1 (33.3) | 0 | 5 (22.7) | 0 |
| Nausea | 0 | 0 | 1 (16.7) | 0 | 1 (33.3) | 0 | 1 (14.3) | 0 | 1 (33.3) | 0 | 4 (18.2) | 0 |
| Rash | 0 | 0 | 1 (16.7) | 0 | 1 (33.3) | 0 | 2 (28.6) | 1 (14.3) | 0 | 0 | 4 (18.2) | 1 (4.5) |
| Amylase increased | 1 (33.3) | 1 (33.3) | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (9.1) | 1 (4.5) |
| Anemia | 0 | 0 | 0 (0.0) | 0 | 1 (33.3) | 0 | 1 (14.3) | 0 | 0 | 0 | 2 (9.1) | 0 |
| Dry skin | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 1 (33.3) | 0 | 2 (9.1) | 0 |
| Hemoglobin decreased | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 2 (9.1) | 0 |
| Rash, follicular | 1 (33.3) | 0 | 0 (0.0) | 0 | 1 (33.3) | 0 | 0 | 0 | 0 | 0 | 2 (9.1) | 0 |
| Rash, pustular | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 2 (9.1) | 0 |

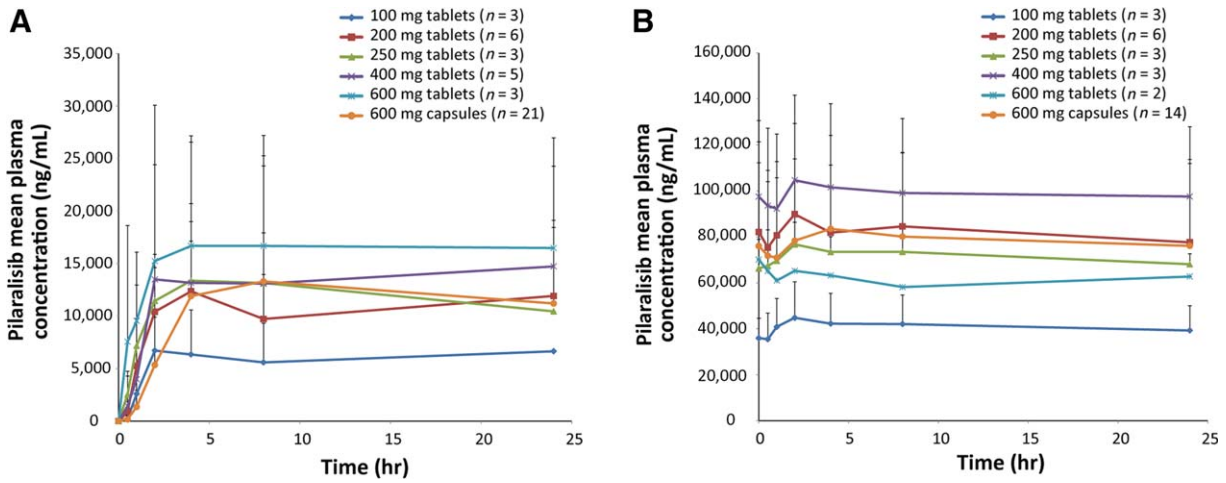


**Figure 1.** Mean (+ standard deviation [SD]) plasma concentration of pilaralisib administered once daily in patients with solid tumors on Cycle 1, Day 1 **(A)**, and Cycle 1 Day 28 **(B)**. SD was not calculable for 100 mg and 250 mg tablets at Cycle 1, Day 1, for the 24-hour time point or for 600 mg tablets at Cycle 1, Day 28 ($n = 2$ for each).

In PK analyses, pilaralisib plasma exposure did not appear to increase in a dose-proportional manner and steady-state plasma exposure appeared to be slightly higher with pilaralisib 400 mg tablets compared with capsules at 400 mg and 600 mg once daily (Fig. 1); however, small patient numbers prevented firm conclusions. Pharmacodynamic impact on glucose homeostasis was evaluated in plasma samples from patients receiving pilaralisib tablets at 250, 400, and 600 mg ($n = 2$, $n = 3$, and $n = 2$, respectively); no impact was observed on C-peptide or glucose levels in the limited sample set analyzed. Similarly, no impact was observed on C-peptide or glucose levels in plasma samples from five patients with lymphoma receiving 600 mg pilaralisib capsules.

Of 18 evaluable patients, two patients (11.1%) had a PR (overall response rate 11.1%) and six patients (33.3%) had stable disease as best response. Median progression-free survival was 1.9 months (90% confidence interval 1.7–5.5); three patients (16.7%) were alive and progression free at 6 months.

Based on PK data, the recommended phase II dose of pilaralisib tablets was established as 400 mg once daily.

| Trial Information | |
|---|---|
| **Disease** | Advanced cancer/Solid tumor only |
| **Stage of Disease/Treatment** | Metastatic/Advanced |
| **Prior Therapy** | No designated number of regimens |
| **Type of Study – 1** | Phase I |
| **Type of Study – 2** | Null |
| **Primary Endpoint** | Maximum tolerated dose |
| **Primary Endpoint** | Toxicity |
| **Secondary Endpoint** | Pharmacokinetics |
| **Secondary Endpoint** | Pharmacodynamic |
| **Secondary Endpoint** | Efficacy |
| **Additional Details of Endpoints or Study Design**<br>This was a phase I, multicenter, open-label, single-arm study. The primary endpoints were MTD and safety. Secondary or exploratory endpoints included pharmacokinetics, pharmacodynamics, and efficacy. Eligible patients were aged $\geq$18 years, with an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2 and histologically confirmed metastatic or unresectable solid tumors. Patients were required to have adequate organ and bone marrow function, fasting plasma glucose $<$160 mg/dL, and hemoglobin A1c $<$8%. Patients who had previously received treatment with a PI3K inhibitor were excluded. All patients provided written informed consent. | |
| **Panel for Copy Number Alterations in Squamous Non-Small Cell Lung Cancer**<br>DNA was isolated from macrodissected, 5-micron, formalin-fixed, paraffin-embedded tumor tissue sections enriched for 50% tumor cell content, using standard protocols. DNA was analyzed by droplet digital polymerase chain reaction (ddPCR; BioRad, Mountain View, CA) for copy number amplifications at the following 12 genic loci: *BCL2*, *CCND1*, *CDK4*, *EGFR*, *ERBB2*, *FGFR1*, *FGFR2*, *FGFR3*, *FGFR4*, *MET*, *PDGFRA*, and *PIK3CA*. Two locus-specific TaqMan minor groove binder probes (ThermoFisher Scientific, Waltham, MA) were used to measure the concentration of target-specific gene sequences relative to the concentration of reference loci. Quantification of these concentrations provided a ratio of the target to reference loci and was expressed as an absolute copy number. To minimize aneusomy at the reference loci, the reference locus (RPP30, c.16_c.77, chr10q23) was interrogated against two additional reference loci (AP3B1, c.2578–23605_c.2578_23543, chr5q14; NFAT5, c.327_c.395, chr16q22) such that each target locus was normalized to the average concentration of the three reference loci. | |
| **Whole-Exome Sequencing**<br>Whole-exome sequencing was performed as previously described [Nat Med 2014;20:682–688]. | |
| **PTEN Immunohistochemistry**<br>Immunohistochemistry for PTEN was performed using clone 138G6 (Cell Signaling Technology, Danvers, MA) within a Clinical Laboratory Improvement Amendments-certified immunohistochemistry lab. PTEN loss was defined as $<$10% tumor cells staining at any intensity [PLoS One 2012; 7:e30427]. | |
| **Investigator's Analysis** | Drug tolerable, hints of efficacy |

| Drug Information for Phase I Pilaralisib | |
|---|---|
| **Drug 1** | |
| **Generic/Working Name** | Pilaralisib |
| **Drug Type** | Small molecule |
| **Drug Class** | PI3 kinase |
| **Dose** | 100–600 mg (tablets) per day |
| **Route** | Oral (p.o.) |
| **Schedule of Administration** | Once daily, continuous 28-day cycles |

| Patient Characteristics for Phase I Pilaralisib | |
|---|---|
| **Number of Patients, Male** | 8 |
| **Number of Patients, Female** | 14 |
| **Stage** | Stage II — 1<br>Stage III — 2<br>Stage IIIA — 2<br>Stave IV — 9<br>Unknown stage — 8 |
| **Age** | Median (range), years: 63.0 (27–86) |

| | |
|---|---|
| **Number of Prior Systemic Therapies** | Median (range): 3.0 (0–12)<br>0–1 prior systemic therapies — 2 patients<br>2–4 prior systemic therapies — 14 patients<br>≥5 prior systemic therapies — 6 patients |
| **Performance Status: ECOG** | 0 — 10<br>1 — 12<br>2 —<br>3 —<br>Unknown — |
| **Other** | |
| **Median Time from Initial Diagnosis** | Years (range): 2.63 (0.8–14.2) |
| **Patients with Prior Anticancer Treatment** | Prior systemic anticancer therapy alone — 11<br>Prior radiation therapy alone — 1<br>Prior systemic anticancer therapy or radiation — 22<br>Both prior systemic anticancer therapy and radiation — 10 |

| Cancer Types or Histologic Subtypes | |
|---|---|
| **Adenocarcinoma** | 6 |
| **Bladder cancer** | 1 |
| **Carcinosarcoma** | 1 |
| **Chordoma (pelvis)** | 1 |
| **Colorectal adenocarcinoma** | 1 |
| **Ductal with lobular component (breast)** | 1 |
| **Endometrial cancer** | 3 |
| **Leiomyosarcoma (uterus)** | 1 |
| **Mesothelioma** | 2 |
| **Non-small cell lung cancer** | 2 |
| **Ovarian carcinoma** | 1 |
| **Prostate cancer** | 1 |
| **Sarcoma (synovial)** | 1 |

| Primary Assessment Method for Phase I Pilaralisib | |
|---|---|
| **Number of Patients Enrolled** | 22 |
| **Number of Patients Evaluable for Toxicity** | 22 |
| **Number of Patients Evaluated for Efficacy** | 18 |
| **Evaluation Method** | RECIST 1.0 |
| **Response Assessment CR** | 0% |
| **Response Assessment PR** | 11.1% |
| **Response Assessment SD** | 33.3% |
| **Response Assessment PD** | 55.6% |
| **(Median) Duration Assessments PFS** | 1.9 months; CI, 1.7–5.5 |
| **(Median) Duration Assessments Duration of Treatment** | 56.0 days |

| Assessment, Analysis, and Discussion | |
|---|---|
| **Completion** | Study completed |
| **Investigator's Assessment** | Drug tolerable, hints of efficacy |

The phosphoinositide 3-kinase (PI3K) pathway is pivotal in the growth and survival of normal cells, and dysregulation of this pathway has been implicated in the pathogenesis of various solid tumors [1–3]. Several PI3K inhibitors in development have shown antitumor activity in patients with advanced solid tumors [4–6].

Pilaralisib is a highly selective and reversible pan-class I PI3K inhibitor. This single-arm study was part of a multicenter, open-label, phase I study (NCT00486135), investigating single-agent pilaralisib capsules in patients with advanced solid tumors, which established the maximum tolerated dose (MTD) for the capsule formulation at 600 mg once daily (QD) [5]. Pharmacodynamic analyses demonstrated that pilaralisib treatment inhibited the PI3K pathway, and one patient with advanced non-small cell lung cancer had a partial response (PR). The cohort described in this report investigated a tablet formulation of pilaralisib. Primary endpoints were MTD and safety. Secondary and exploratory endpoints included pharmacokinetics (PK), pharmacodynamics and efficacy.

In total, 22 patients with solid tumors received pilaralisib tablets QD at 100 mg ($n = 3$), 200 mg ($n = 6$), 250 mg ($n = 3$), 400 mg ($n = 7$), or 600 mg ($n = 3$). Median age was 63.0 years (range 27–86), and median number of prior systemic therapies was 3 (range 0–12). All 22 patients discontinued study treatment. The most common reasons for study discontinuation were disease progression as defined by RECIST version 1.0 (15 patients, 68.2%), disease progression based on clinical deterioration (three patients, 13.6%), and adverse event (AE; two patients, 9.1%). One patient was enrolled into an extension study (TED12414).

The mean ($\pm$ standard deviation) duration of exposure was 158.0 days ($\pm$258.97 days) and ranged from 6 to 1,009 days. Median duration of exposure was 56.0 days. Median number of cycles received was 2 (range 1–36). The majority of patients (90.9%) received $>$90% of the planned doses of pilaralisib.

No dose-limiting toxicities were reported. Treatment-related grade $\geq$3 AEs reported were increased alanine aminotransferase, increased amylase, increased aspartate aminotransferase, diarrhea, increased gamma-glutamyl transferase, increased lipase, and rash (one patient each, all grade 3). Hepatic toxicity was reported in six patients (27.3%) and was grade $\geq$3 in four patients (18.2%). There were no events of bilirubin increased and no cases of Hy's law. There was no evidence of cardiovascular toxicity as determined in ECG assessments. Seven patients (31.8%) reported one or more serious AEs (SAEs), of which only disease progression (three patients, 13.6%) was reported in more than one patient. All SAEs were assessed to be either not related or unlikely to be related to treatment. Six patients (27.3%) had one or more AEs leading to a dose delay or interruption. Two patients (9.1%) permanently discontinued treatment because of an AE (grade 5 encephalopathy and grade 4 ischemic stroke); both AEs were not treatment related. No deaths occurred during the study; there were four deaths within 30 days after the last dose of study drug, all related to disease progression.

Figure 1 shows the mean pilaralisib plasma concentration-time profile after the first single dose on Cycle 1, Day 1, and repeated daily dosing at Cycle 1, Day 28. After repeated daily administration of pilaralisib tablets (100–600 mg), steady state was reached by Cycle 1, Day 28, and median time to maximum concentration ranged from 1.99 to 23.1 hours (Table 2). The mean accumulation ratio for maximum concentration ($C_{max}$) and area under the curve ($AUC_{0–24}$) for Cycle 1, Day 28, compared with Cycle 1, Day 1, ranged from 5.9-fold to 10.3-fold and 3.1-fold to 9.9-fold, respectively. Exposure ($C_{max}$ and $AUC_{0–24}$) did not appear to increase dose proportionally for the 100–600 mg dose levels, but conclusions were limited by the small patient numbers. On Cycle 1, Day 28, exposure was higher with pilaralisib 400 mg tablets administered QD compared with 600 mg tablets QD and the capsule formulation administered at 400 mg and 600 mg QD (mean $AUC_{0–24}$ 2,820,000 [$n = 2$] vs. $AUC_{0–24}$ 1,470,000 [$n = 2$], 2,653,000 [$n = 2$] and 1,930,000 ng $\times$ h/mL [$n = 14$], respectively).

The impact of pilaralisib tablets on glucose homeostasis was evaluated in post-dose plasma samples after overnight fasting (up to 2 hours after dosing) on Days 1, 8, and 28. Pilaralisib had no effect on glucose and C-peptide levels. No differences were observed between the capsule and tablet formulation.

Of 18 evaluable patients, two patients (11.1%) had a PR (overall response rate 11.1%): a female patient aged 53 years with poorly differentiated vaginal adenocarcinoma who had progression-free survival (PFS) of 33.0 months (200 mg cohort; Fig. 2), and a female patient aged 41 years with squamous cell lung carcinoma who had PFS of 27.6 months (250 mg cohort). A squamous lung cancer copy number panel performed on a prior pneumonectomy specimen demonstrated *PIK3CA* amplification (copy number alteration 4.6; $>$4 considered amplified), with weak focal staining for PTEN in tumor cells. Mutational analysis on whole exome sequencing demonstrated *TP53* P151H, *KRAS* T20M, and *PIK3C2B* R296Q. A supraclavicular lymph node biopsy performed after progression was inadequate for genomic analyses, but tumor cells identified were negative for PTEN staining. *PIK3CA* amplification, coupled with PTEN loss and *PIK3C2B* mutation [7], possibly caused PI3K dependence that resulted in the clinical benefit observed. The patient had PR at 11.6 months, maintained for 16 months (maximum reduction in tumor burden 50.3%). Six patients (33.3%) had stable disease as best response. Median PFS was 1.9 months (90% confidence interval 1.7–5.5); three patients (16.7%) were alive and progression free at 6 months.

In summary, pilaralisib tablets were associated with a favorable safety profile, similar to that observed in patients who received the capsule formulation [5]. The most common treatment-related toxicities included gastrointestinal toxicities, fatigue, and hyperglycemia (Table 1), consistent with other PI3K inhibitors in clinical development [4, 6, 8–11]. Steady-state plasma exposure was higher with pilaralisib 400 mg tablets than with 400 and 600 mg capsules [5]. Neither tablets nor capsules affected glucose homeostasis [5]. Pilaralisib tablets showed preliminary antitumor activity, including two PRs. The MTD for pilaralisib tablets was not determined and the recommended phase II dose, based on PK data, is 400 mg QD.

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## Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/ inventor/patent holder; (SAB) Scientific advisory board


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## Figures and Tables

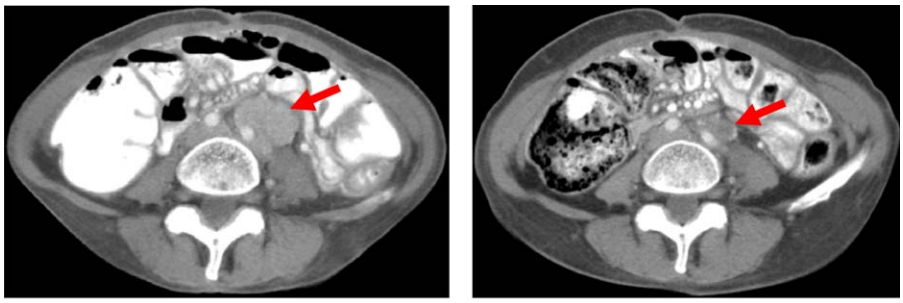


**Figure 2.** Partial response in a patient aged 54 years with poorly differentiated vaginal adenocarcinoma treated with pilaralisib tablets 200 mg once daily. Sequential computed tomography scans of the abdomen show a 32% interval reduction of a left para-aortic soft tissue mass in Cycle 8, compared with baseline. Overall tumor reduction was 21% in Cycle 8.

**Table 2.** Pilaralisib pharmacokinetic parameters in patients with solid tumors. Mean ± standard deviation (geometric mean) [% coefficient of variation]

| Parameter | Pilaralisib tablets, once-daily dose | | | | | Pilaralisib capsules 600 mg once daily |
|---|---|---|---|---|---|---|
| | 100 mg | 200 mg | 250 mg | 400 mg | 600 mg | |
| Cycle 1, Day 1 | | | | | | |
| *n* | 3 | 6 | 3 | 5 | 3 | 21 |
| $C_{max}$, ng/mL | 7,050 ± 4,870 (5,220) [69.1] | 13,000 ± 6,500 (11,500) [50.1] | 14,300 ± 4,300 (13,900) [30.0] | 17,300 ± 13,900 (14,000) [80.1] | 18,300 ± 11,100 (15,100) [60.6] | 13,900 ± 10,800 (10,300) [77.9] |
| $t_{max}$,[a] h | 3.95 (2.00–4.00) | 3.06 (2.00–25.22) | 2.05 (2.00–8.00) | 8.00 (2.00–24.05) | 23.12 (2.00–24.00) | 8.00 (2.00–24.00) |
| $AUC_{0-24}$, ng × h/mL | 174,000 ± NC (174,000) [NC][b] | 272,000 ± 147,000 (239,000) [54.1] | 253,000 ± NC (249,000) [NC][b] | 361,000 ± 276,000 (292,000) [76.6][c] | 515,000 ± NC (511,000) [NC][b] | 251,000 ± 193,000 (184,000) [76.9] |
| Cycle 1, Day 28 | | | | | | |
| *n* | 3 | 6 | 3 | 3 | 2 | 14 |
| $C_{max}$, ng/mL | 45,300 ± 14,800 (43,600) [32.6] | 92,100 ± 38,100 (84,300) [41.4] | 77,700 ± 9,430 (77,300) [12.1] | 105,000 ± 36,600 (99,800) [34.9] | 71,900 ± NC (71,300) [NC] | 87,200 ± 40,300 (75,800) [46.3] |
| $t_{max}$,[a] h | 2.00 (2.00–8.23) | 1.99 (0.00–8.12) | 2.05 (0.00–4.00) | 2.02 (2.00–21.30) | 4.00 (0.00–8.00) | 4.00 (0.00–8.00) |
| $AUC_{0-24}$, ng × h/mL | 988,000 ± 292,000 (957,000) [29.5] | 2,110,000 ± 791,000 (1,960,000) [37.4][d] | 1,720,000 ± 105,000 (1,720,000) [6.1] | 2,820,000 ± NC (2,820,000) [NC][e] | 1,470,000 ± NC (1,460,000) [NC] | 1,930,000 ± 913,000 (1,670,000) [47.3] |
| Rac $C_{max}$ (vs. Cycle 1, Day 1) | 10.3 ± 8.4 | 8.5 ± 6.1 | 5.9 ± 2.5 | 8.0 ± 4.3 | 7.3 ± NC | 10.5 ± 4.3 |
| Rac $AUC_{0-24}$ (vs. Cycle 1, Day 1) | 6.6 ± NC[e] | 9.9 ± 7.6[d] | 7.1 ± NC[e] | 7.7 ± NC[e] | 3.1 ± NC[f] | 13.0 ± 6.8 |
| $C_{trough}$, ng/mL | 35,900 ± 8,630 (35,200) [24.0] | 82,100 ± 39,300 (72,500) [47.8] | 66,300 ± 12,700 (65,400) [19.1] | 97,500 ± 33,200 (93,000) [34.0] | 70,100 ± NC (69,200) [NC] | 70,100 ± NC (69,200) [NC] |

[a]Median (range).
[b]$n = 2$.
[c]$n = 4$.
[d]$n = 5$.
[e]$n = 2$.
[f]$n = 1$.
Abbreviations: AUC, area under the curve; $C_{max}$, maximum concentration; $C_{trough}$, trough concentration; NC, not calculated; Rac, accumulation ratio; $t_{max}$, time to maximum concentration.